USAMRIID

United States Army Medical Research Institute of Infectious Diseases

ANTHRAX

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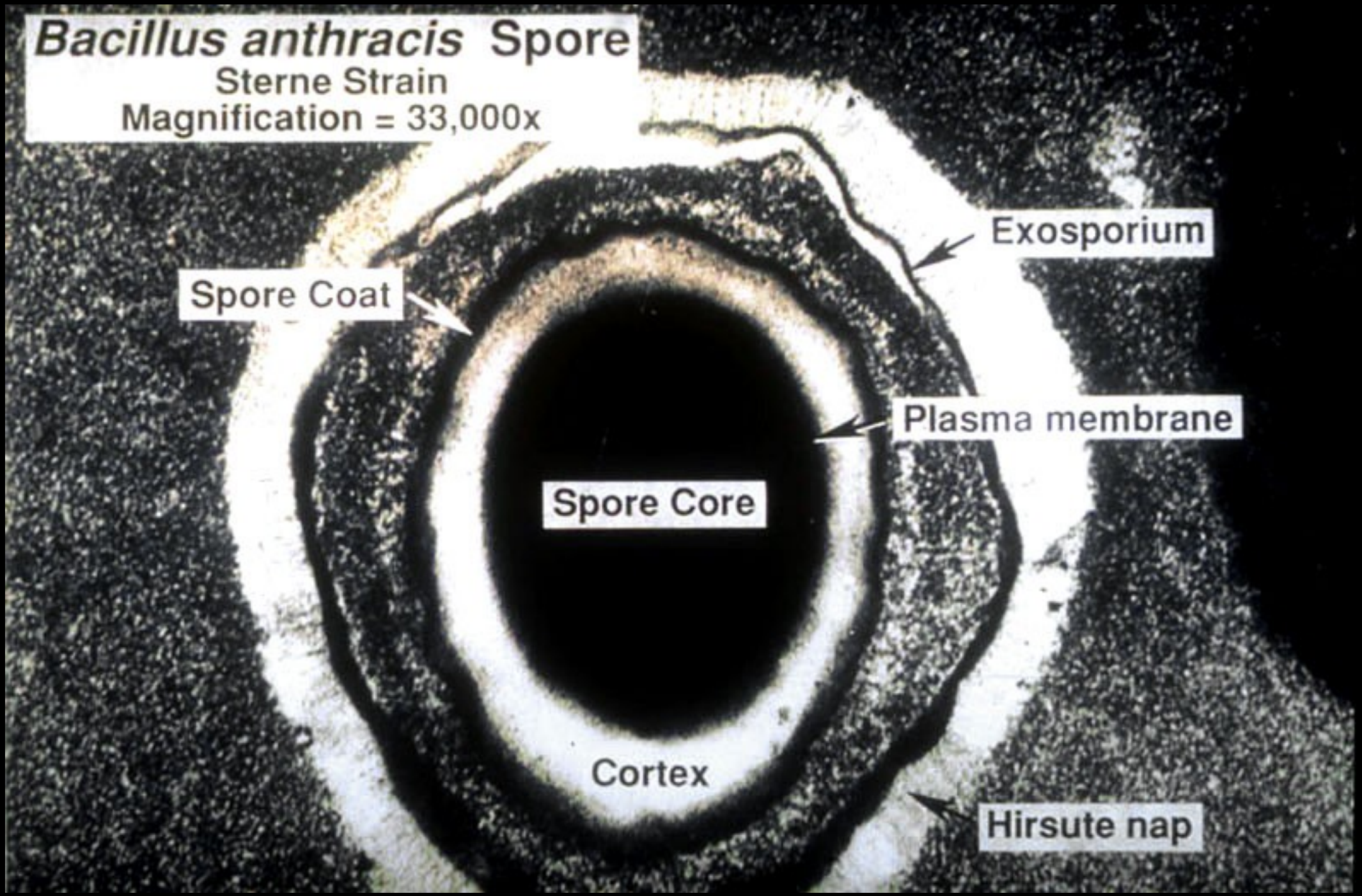
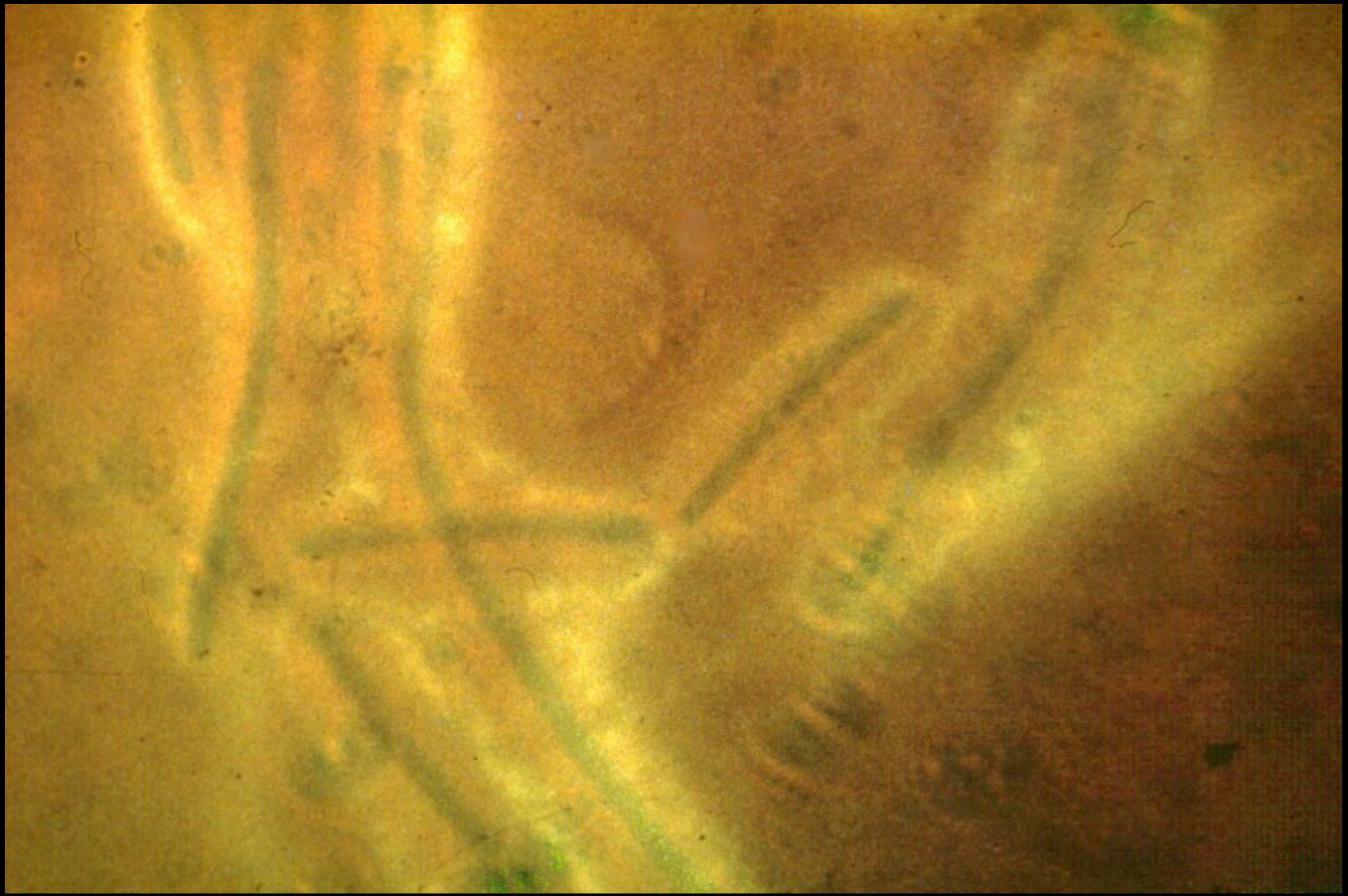
Anthrax
History

- **1491 BC - Fifth plague of Egypt (Exodus Ch. 9)**
- **17th Century - “Black Bane”**
- **1876 - Koch’s postulates**
- **1881 - Pasteur’s attenuated spore vaccine**
- **Late 1800’s - Inhalational anthrax first recognized**

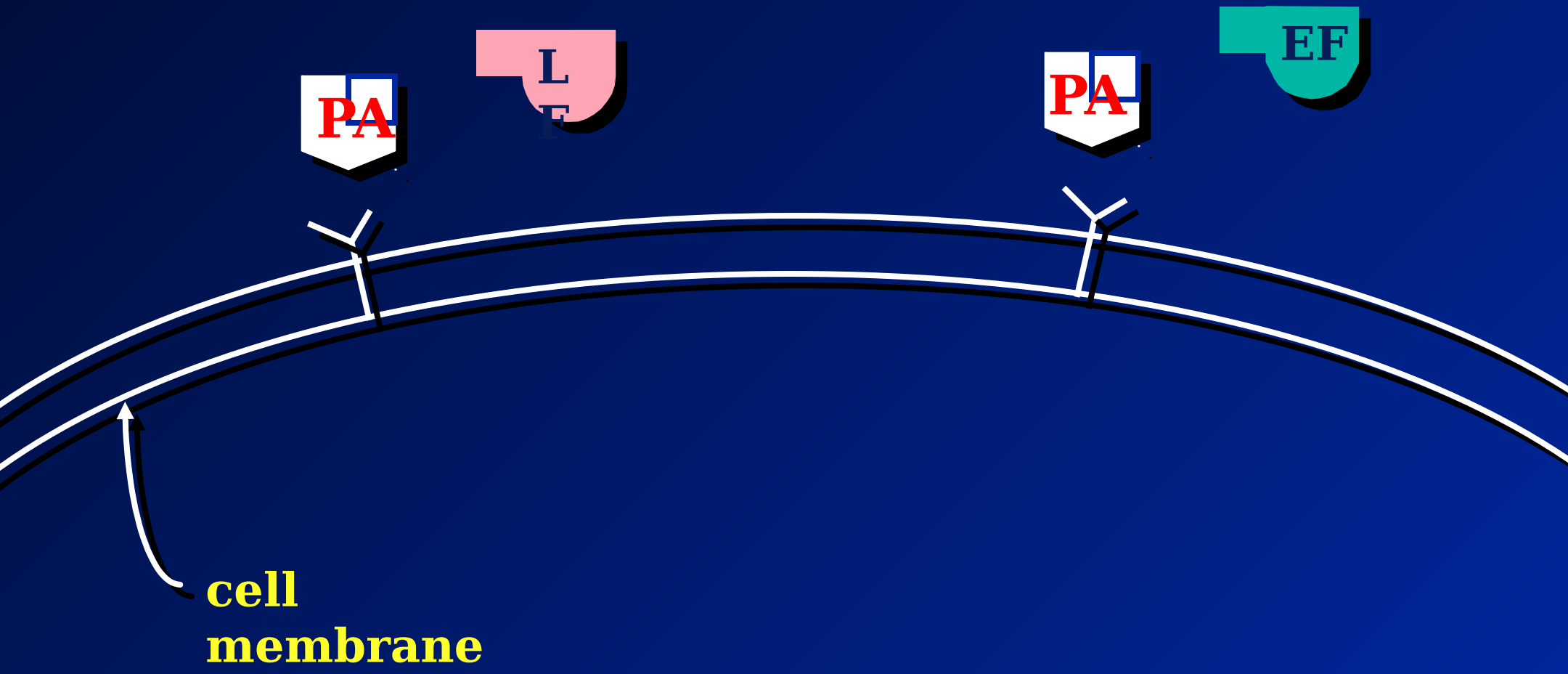
Bacillus anthracis Microbiology

- Gram-positive sporulating bacillus
  - ✓ Sporulates when exposed to oxygen
  - ✓ Spores survive >40 years in soil
- Virulence factors
  - ✓ Polyglutamic acid capsule
  - ✓ Toxins
    - ★ Edema toxin
    - ★ Lethal toxin


Bacillus anthracis Spore
Sterne Strain
Magnification = 33,000x
Exosporium
Spore Coat
Plasma membrane
Spore Core
Cortex
Hirsute nap

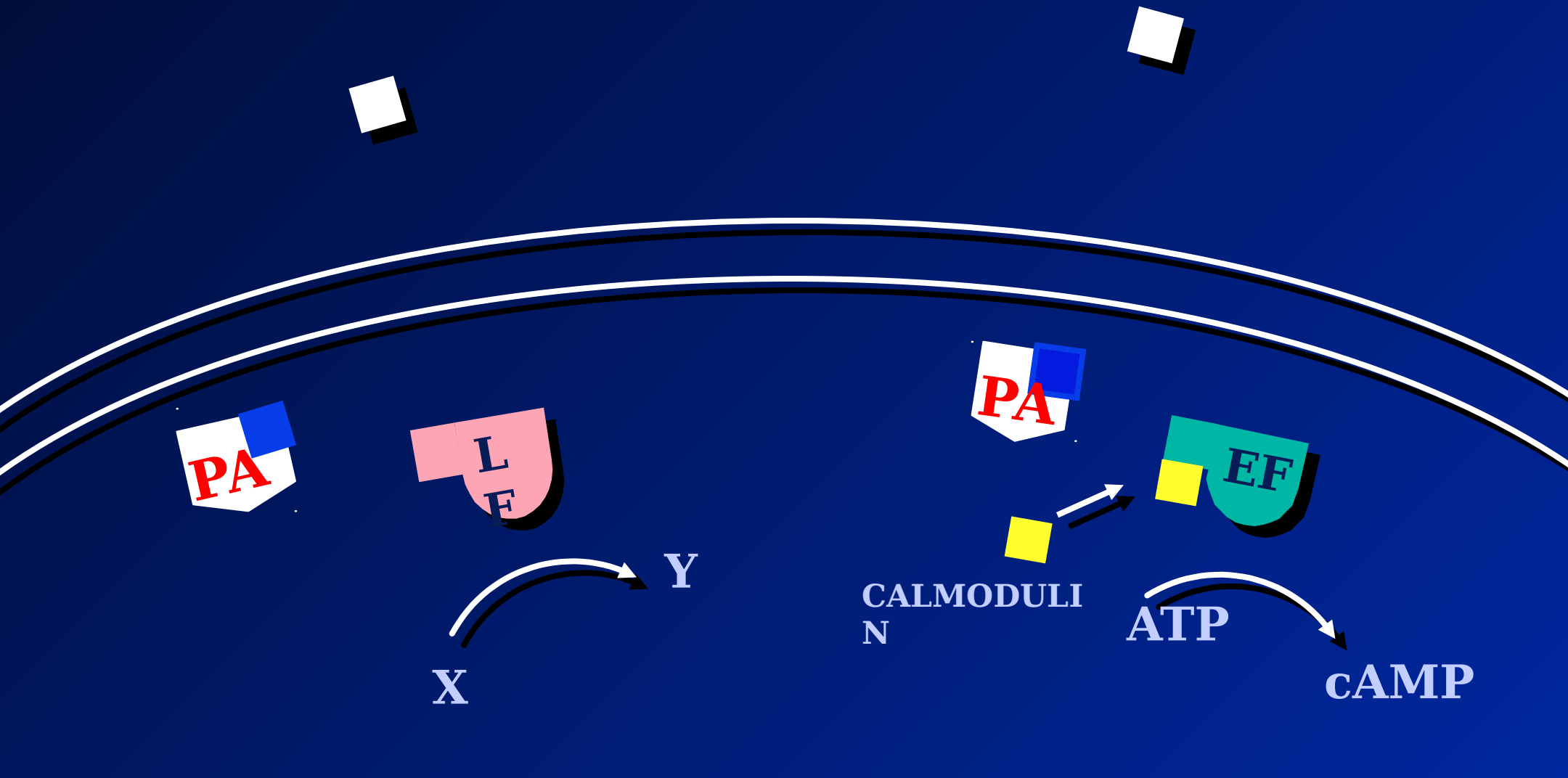


Anthrax Toxins



Anthrax Toxins

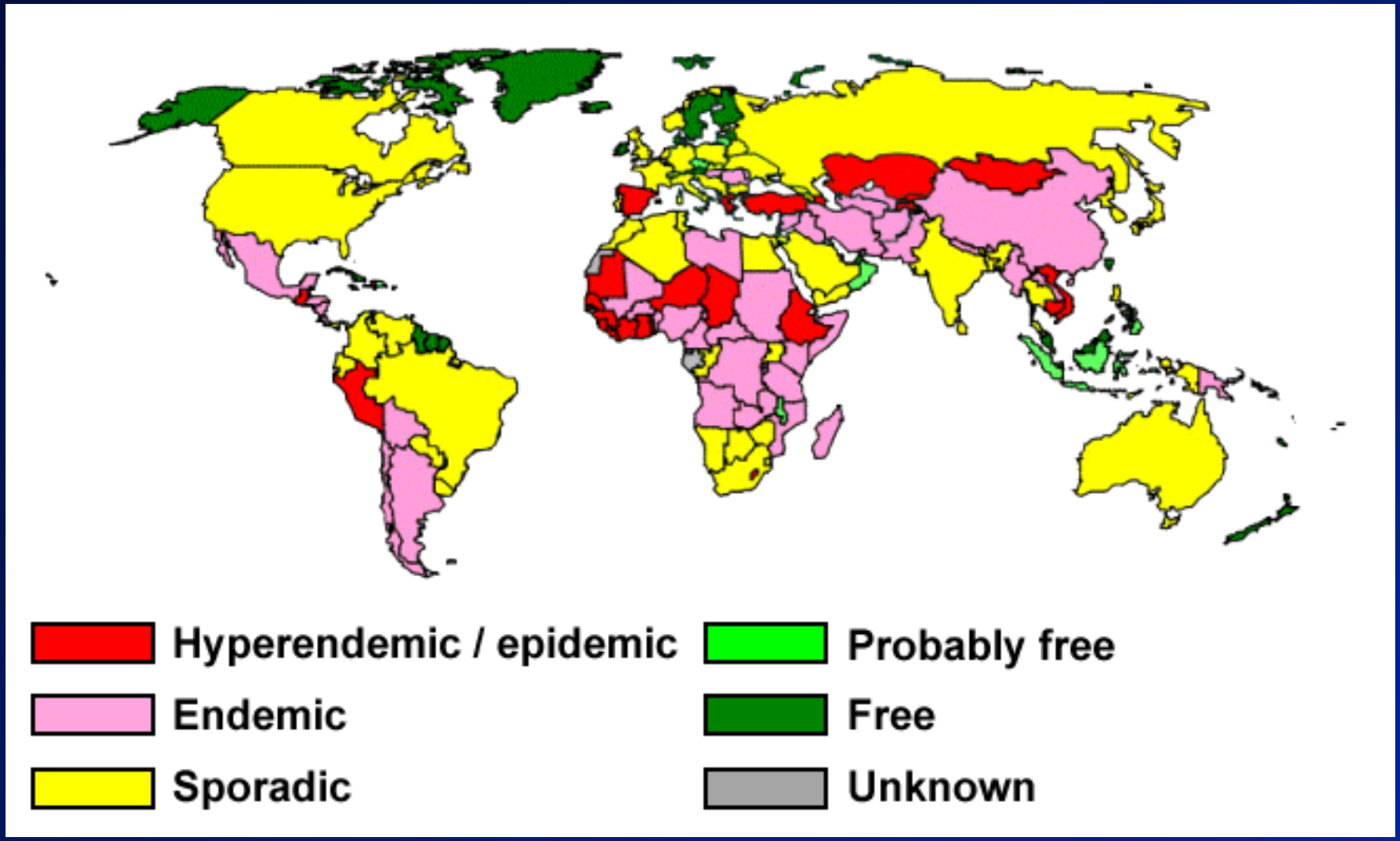
Anthrax Toxins



Anthrax
Epidemiology

- Reservoir: soil
- Worldwide distribution
- Zoonosis: herbivores infected during grazing
- Transmission to humans
  - ✓ contact with infected animals, hides, hair, bone
  - ✓ ingestion of contaminated meat
  - ✓ inhalation in industrial settings
  - ✓ biting and non-biting flies

ANTHRAX


Hyperendemic / epidemic
Endemic
Sporadic
Probably free
Free
Unknown

Anthrax
BW Threat

- Delivered as aerosolized spore form
- Estimated human LD_{50} = 8000-10,000 spores
  - ✓ small volumes (grams) contain tens of thousands LD_{50}'s
- Easily produced in mass quantities
- Efficiently spread over hundreds of square miles
- Weaponized by U.S., Russia, Iraq, others (?)

Anthrax
Pathogenesis

Spores enter skin, GI tract, or lungs

Phagocytized by macrophage

Transported to regional lymph nodes

Germination in macrophages

Replication (doubles in 30 min)

Local production of toxins

Edema & necrosis

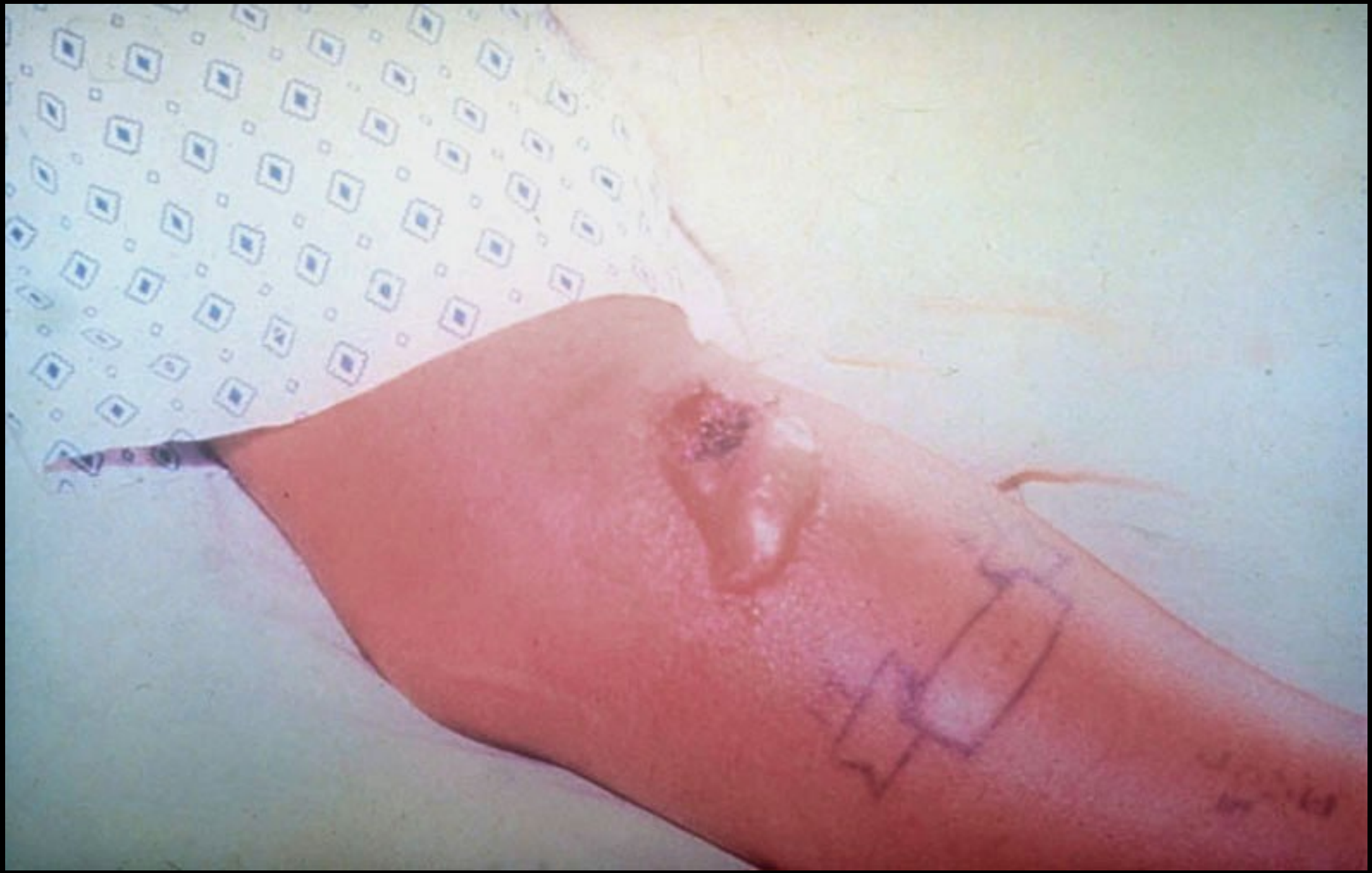
Bacteremia & toxemia

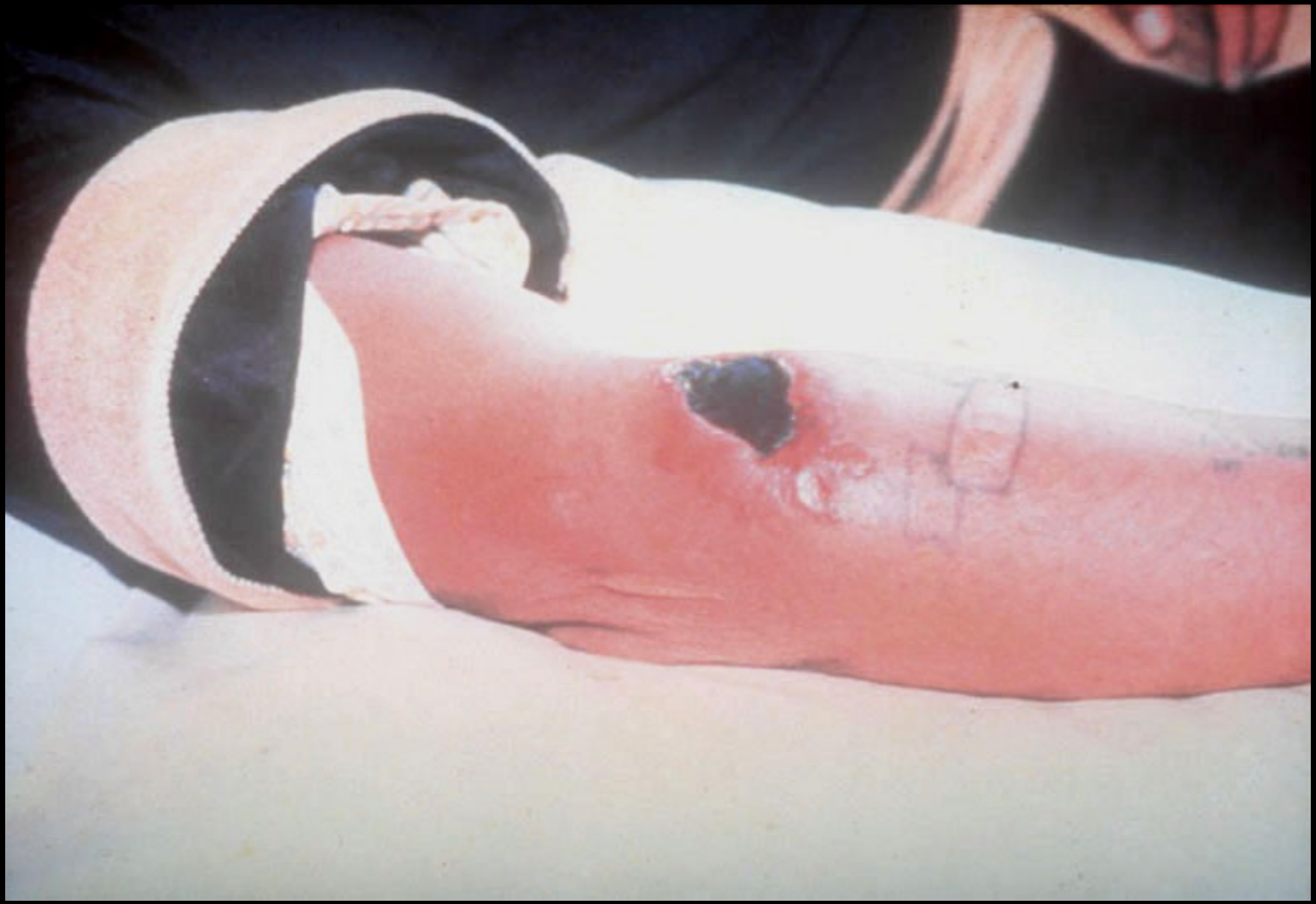
Anthrax
Clinical Manifestations

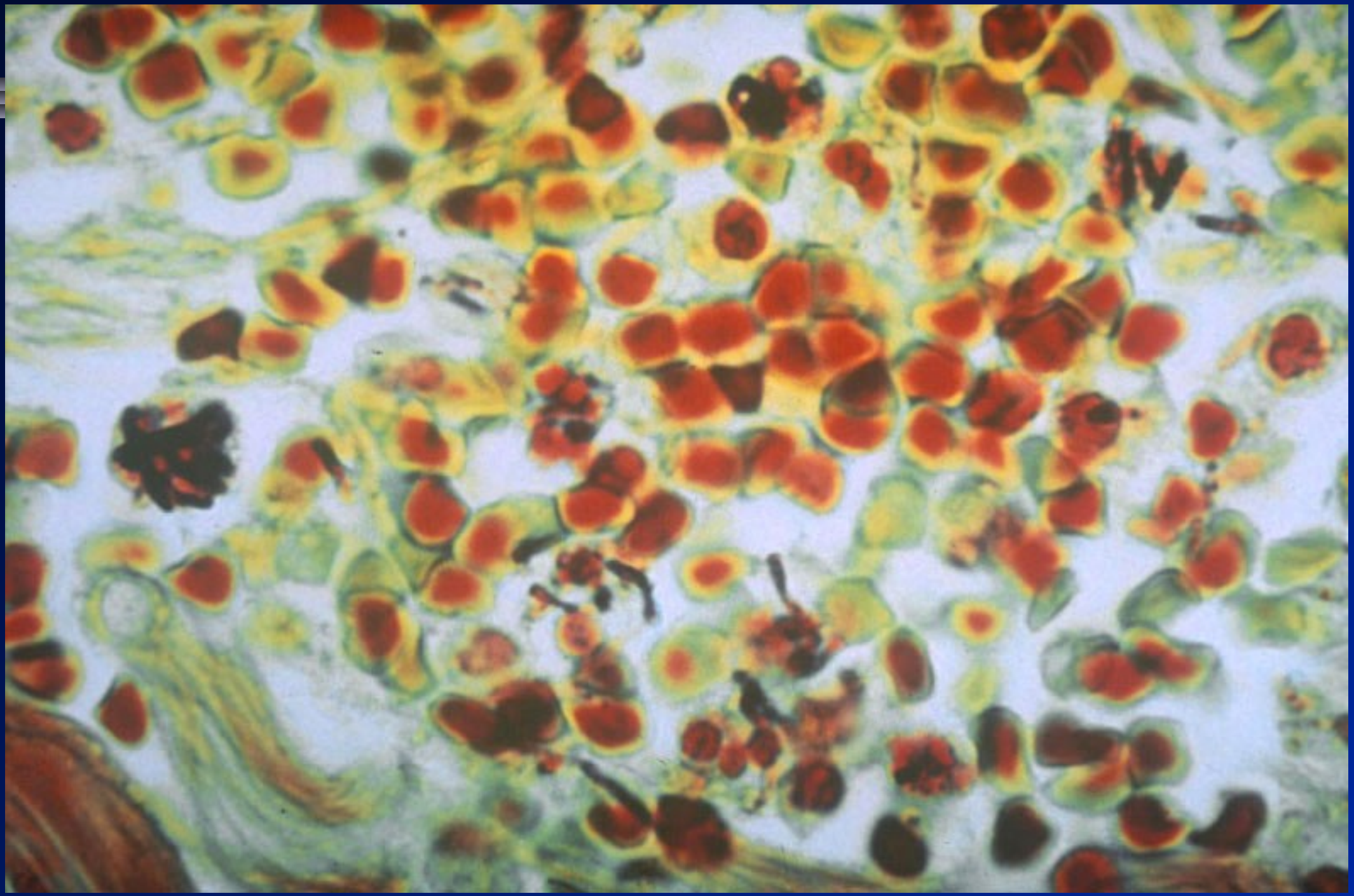
- Cutaneous
- Gastrointestinal
- Inhalational

Cutaneous Anthrax

- >95% of naturally occurring cases
- Spores enter break in skin
  - ✓incubation period 1-5 days
- Papule vesicle ulcer eschar (painless)
  - ✓edema may be massive
  - ✓fever, HA, malaise
- Case fatality rate: untreated ~20%, treated ~1%





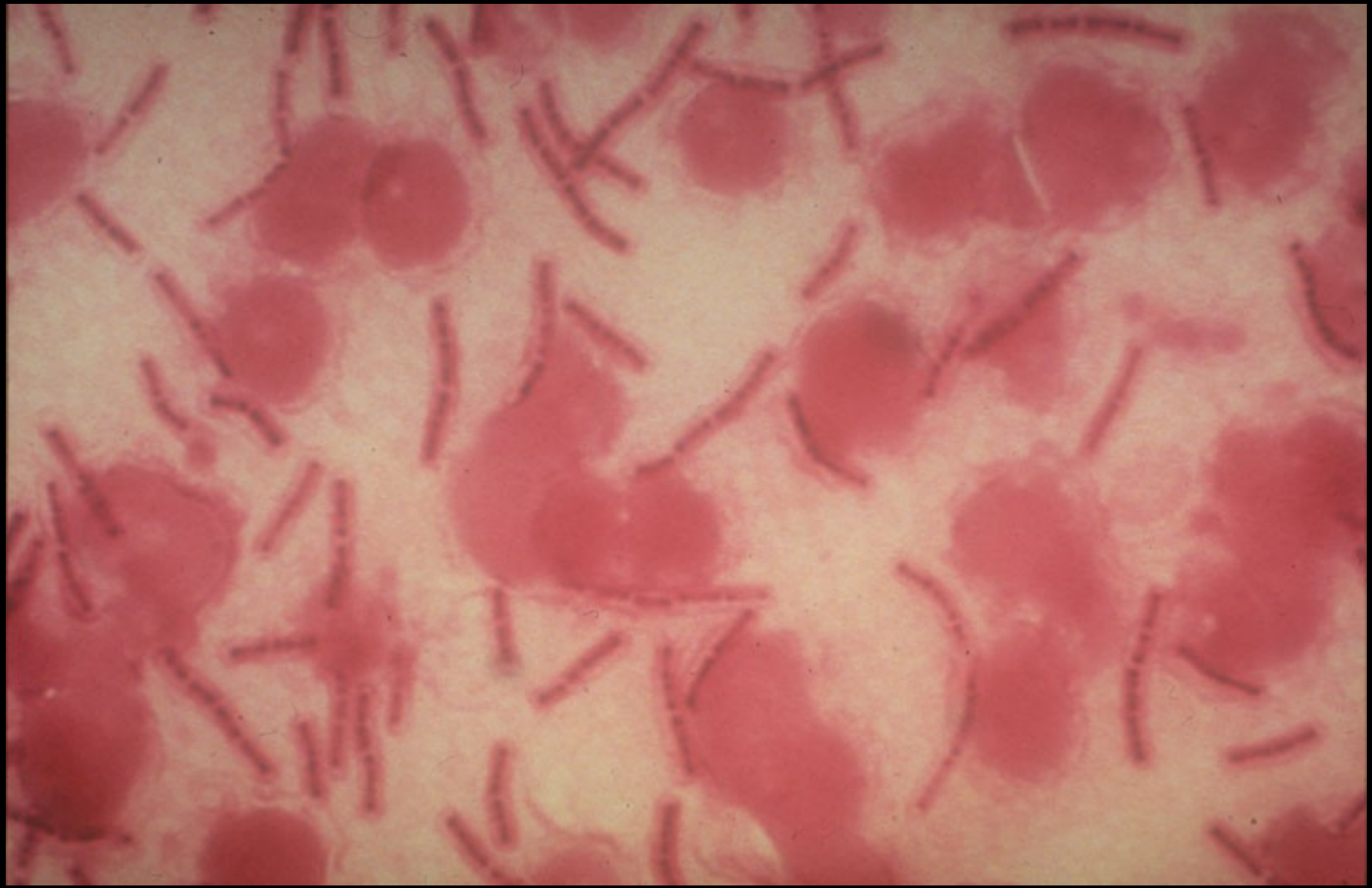


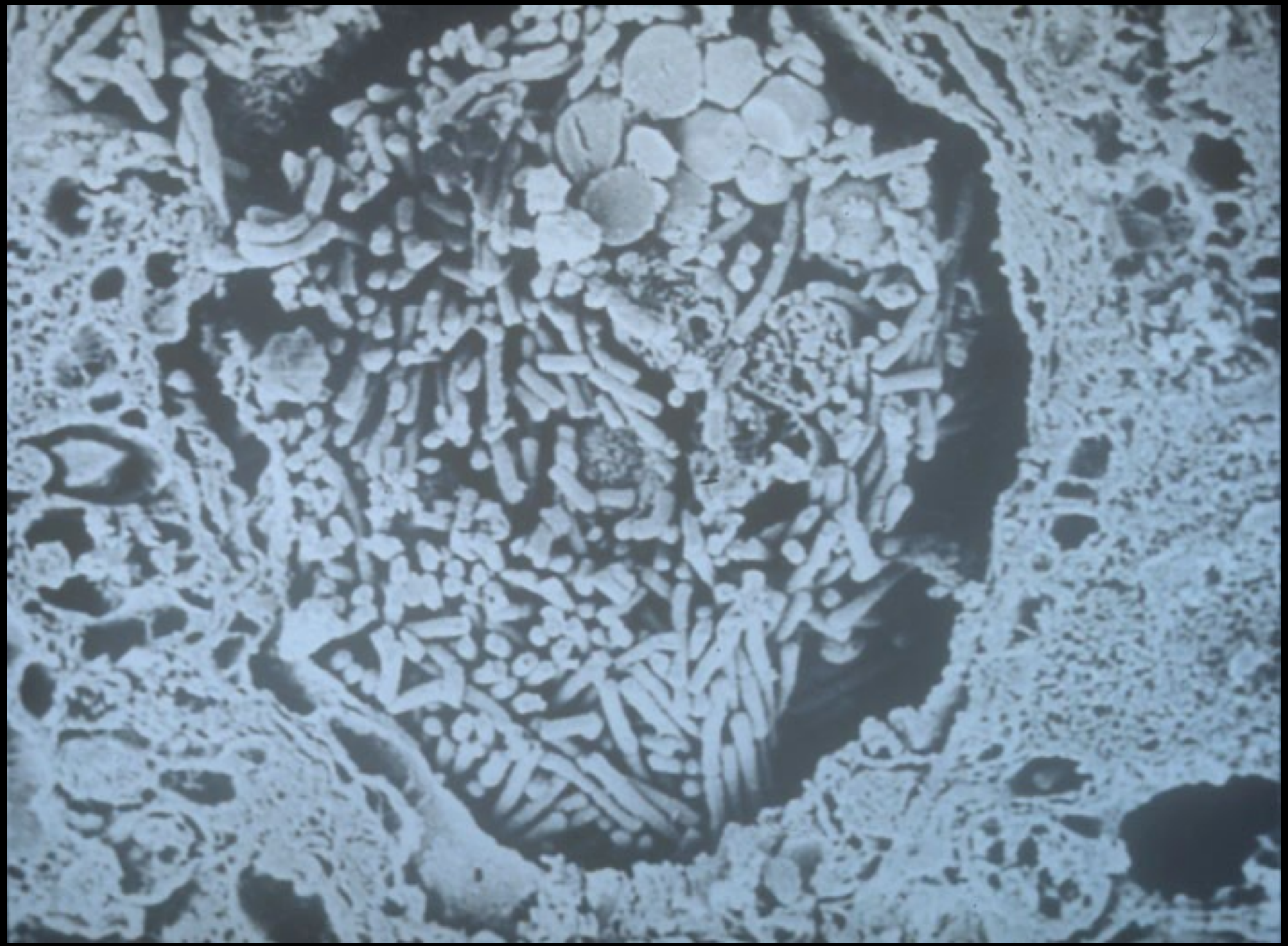
Gastrointestinal Anthrax

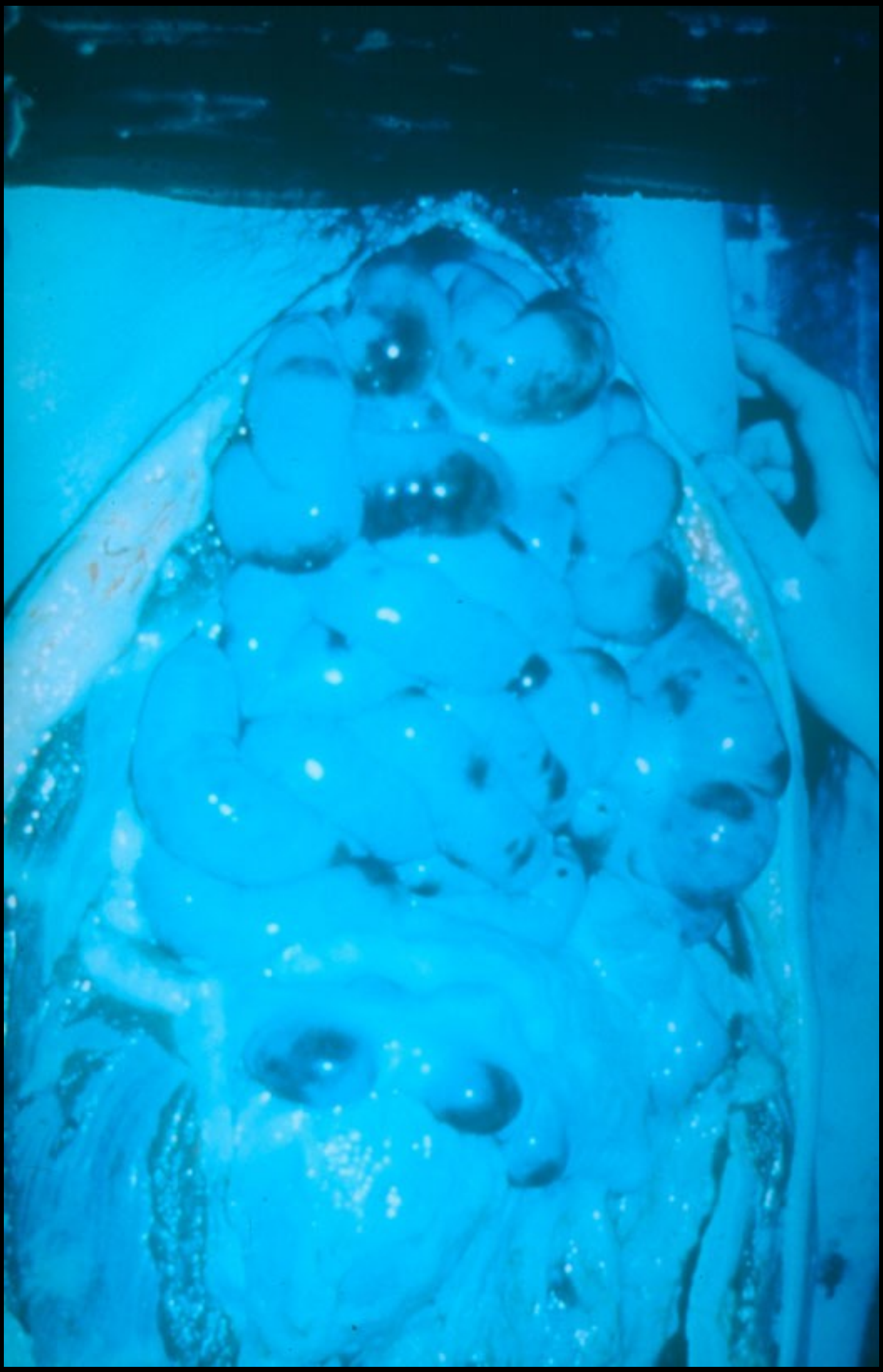
- Insufficiently cooked, contaminated meat
- Nausea, vomiting, fever, severe abdominal pain
  - ✓ may have hematemesis, ascites, diarrhea
- Case fatality rate: 50% +
- Pathology - mucosal ulceration, mesenteric nodes
  - ✓ vs. hematogenous - mult. submucosal lesions

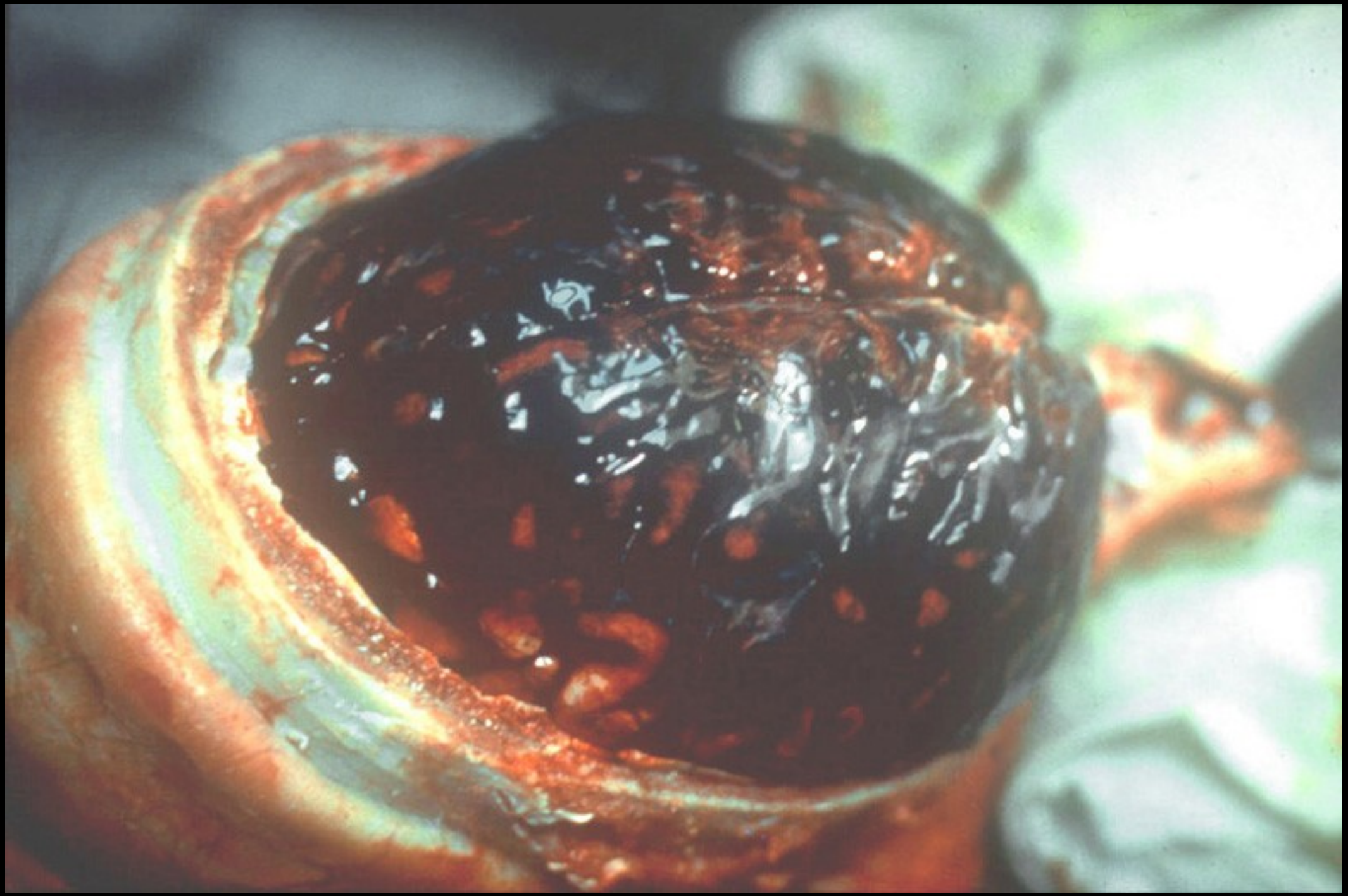
Inhalational Anthrax
Clinical Manifestations

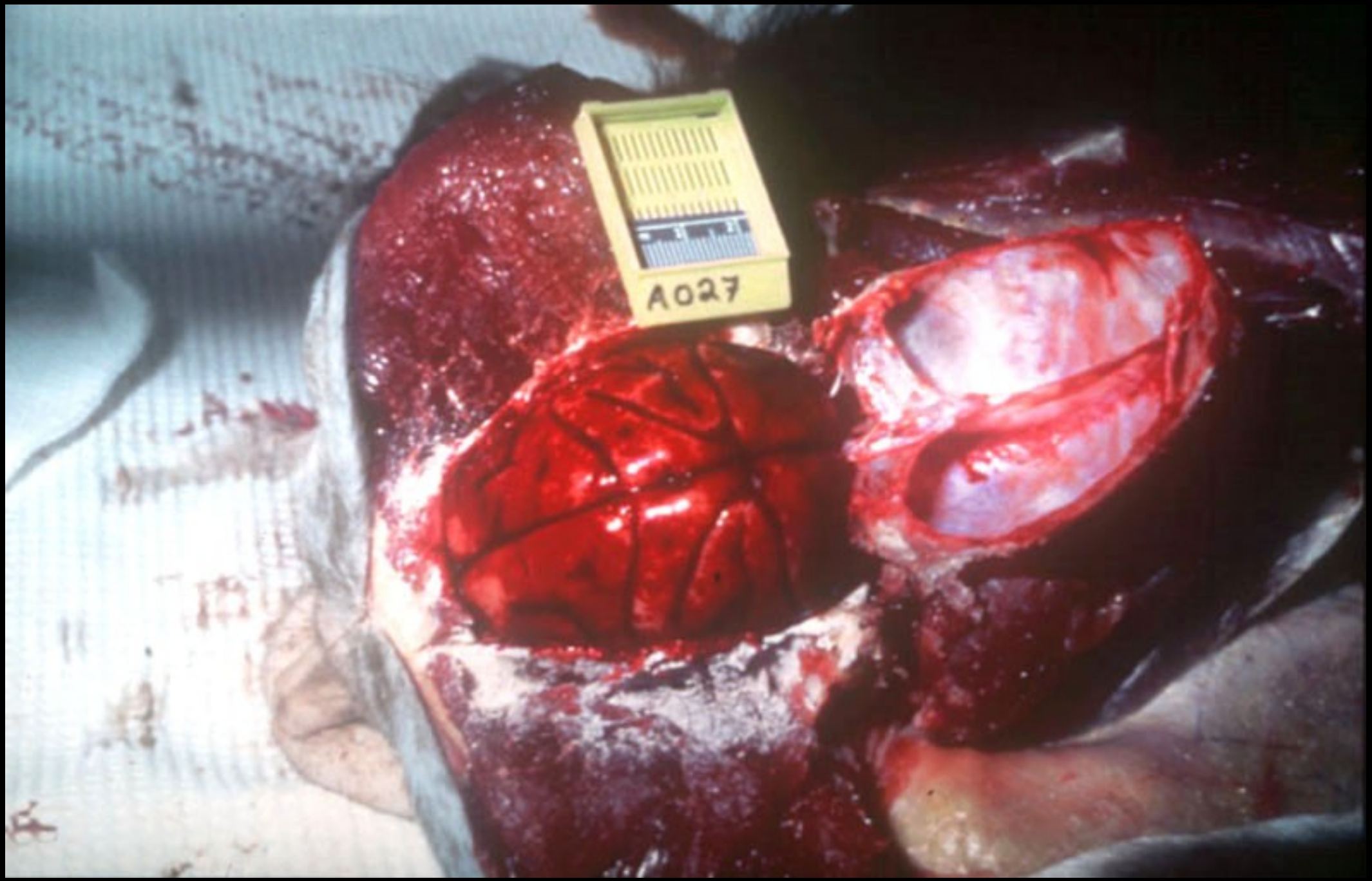
- **Incubation period: 1-6 days**
- **Initial phase: fever, malaise, fatigue; may have non-productive cough; lasts 2-3 days**
- **Terminal phase: abrupt onset of dyspnea, stridor, increased CP, ± chest wall edema**
  - ✓ **rapid progression to cyanosis, shock and death in 24-36 hours**
  - ✓ **widened mediastinum +/- effusion on X-ray**










A027

Anthrax
Typical Inhalational Case

- Day 0: 51 yr old secretary in wool mill visits carding room
- Day 1: weakness, chills, cough. Dx - “viral syndrome”
- Day 2: hospitalized - T 102F, CXR - prominent hilum. Cyanosis develops.
- Day 3: shock, death. Autopsy - hemorrhagic mediastinitis

Inhalational Anthrax
Diagnosis

- High index of suspicion, compatible history
- Development of respiratory distress
  - ✓CXR with widened mediastinum (late)
  - ✓Usually no infiltrates
  - ✓Hemorrhagic pleural effusion or meningitis
- Sputum not helpful
- Blood culture, Gram stain; nasal swab

Anthrax
Diagnosis

- **Lab diagnostic studies**
  - ⋆ **Culture - 1 organism, 8-20 hrs**
  - ⋆ **PCR - 10-100 organisms, 6 hrs**
  - ⋆ **Microscopy - >10,000 cfu/ml, <1 hr**
  - ⋆ **ELISA - 100,000 cfu/ml, 2.5 hrs**
  - ⋆ **Hand-held assays - 100,000 cfu/ml, 15 min**

Henchal, E., USAMRIID Information Paper, 27 JAN 99.

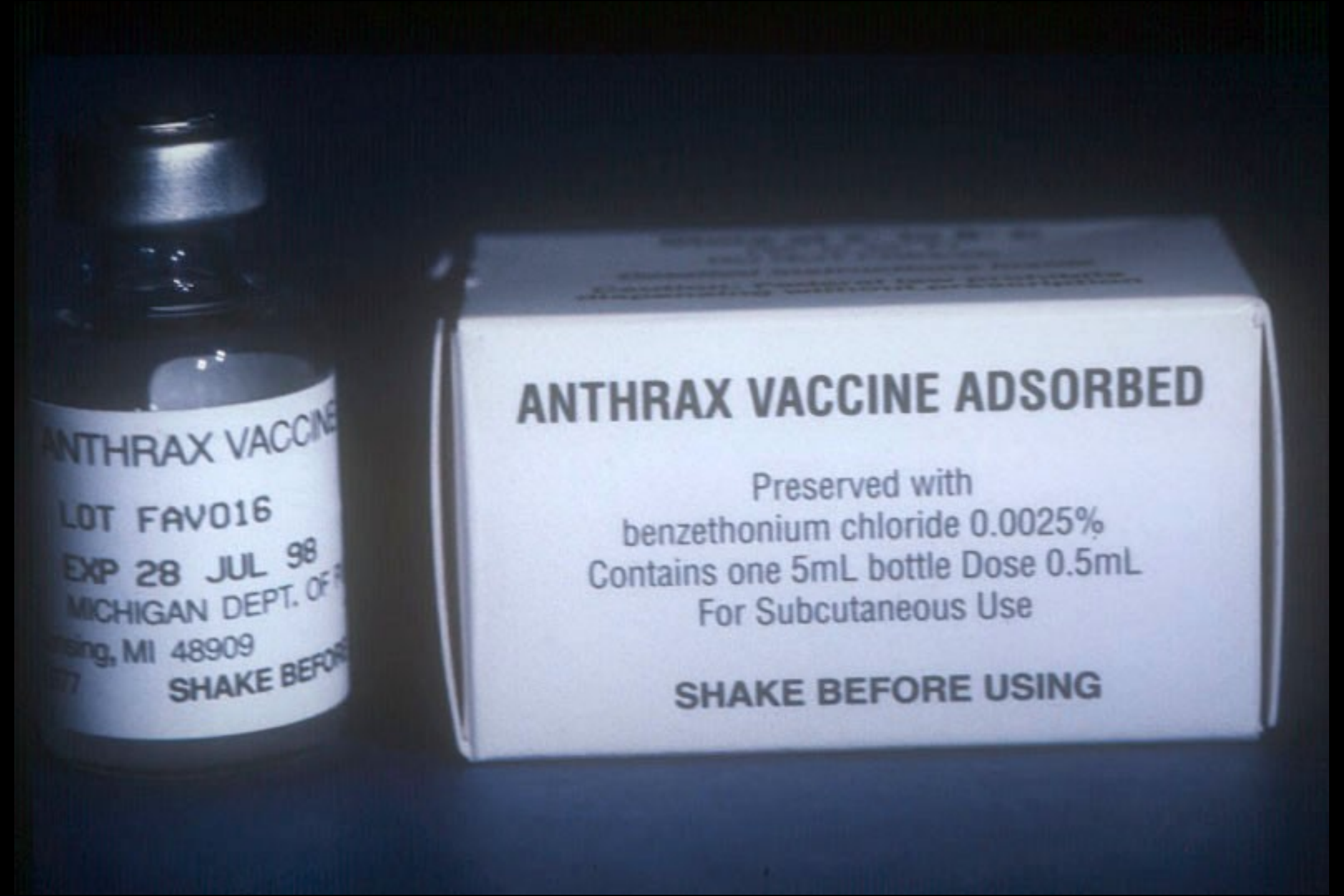
Anthrax
Treatment

- **Penicillin sensitive organisms**
  - ✓**PCN 2 mil Units IV q 2 h**
- **Penicillin resistant or unknown**
  - ✓**Ciprofloxacin 400 mg IV q 8-12 h**
  - ✓**Doxycycline 200 mg then 100 mg IV q 12 h**
- **Debridement of cutaneous lesions contraindicated**
- **Infection control - standard precautions**

Anthrax
Postexposure Prophylaxis

- **Antibiotics**
  - ✓ **Ciprofloxacin 500 mg po BID**
  - ✓ **Doxycycline 100 mg po BID**
  - ✓ **Continue antibiotics for 4 weeks or until 3 doses of vaccine have been received (60 days if no vaccine)**
- **Vaccination - until at least 3 doses are received**

MILES
CIPRO®


NTHRAX VACCINE
LOT FAV016
EXP 28 JUL 98
MICHIGAN DEPT. OF
sing, MI 48909
SHAKE BEFOR
ANTHRAX VACCINE ADSORBED
Preserved with
benzethonium chloride 0.0025%
Contains one 5mL bottle Dose 0.5mL
For Subcutaneous Use
SHAKE BEFORE USING

U.S. Anthrax Vaccine
Safety

- **Animals: 10^9 organisms of vaccine strain given to guinea pigs with no disease**
- **USAMRIID: >12,000 doses given through 1998**
- **MDPH: 25,978 doses**
- **Gulf War Syndrome: >150,000 doses**
  - ✓ Institute of Medicine (1995)
  - ✓ Presidential Advisory Committee (1996)
  - ✓ Lancet, 16 JAN 99

U.S. Anthrax Vaccine
Immunogenicity

- >85% serological response after 1 dose
- >90% seropositive after 3 doses
- 100% develop rise in titer after yearly booster

U.S. Anthrax Vaccine
Efficacy - Animal Trials
Rhesus, Aerosol Challenge, Ames Strain

Study	Regimen	Survival	
*SMB** 1996	0, 2 weeks	20/21	(2 yrs)
*SMB** 1996	0, 4 weeks	9/9	
Unpublished	0, 4 weeks	5/5	
~~*Vaccine* 1998~~	~~One dose~~	~~10/10~~	~~(6 wks)~~
Totals	44/45 (98%)		

*SMB = *Salisbury Medical Bulletin*

U.S. Anthrax Vaccine
Efficacy - Human Trials

- **Field trial with wool mill workers resulted in 92.5% protection against cutaneous anthrax**
- **No cases of inhalational anthrax in vaccinated group, five cases in unvaccinated**

Brachman, P., et. al., American Journal of Public Health, 1962: 52,632-645

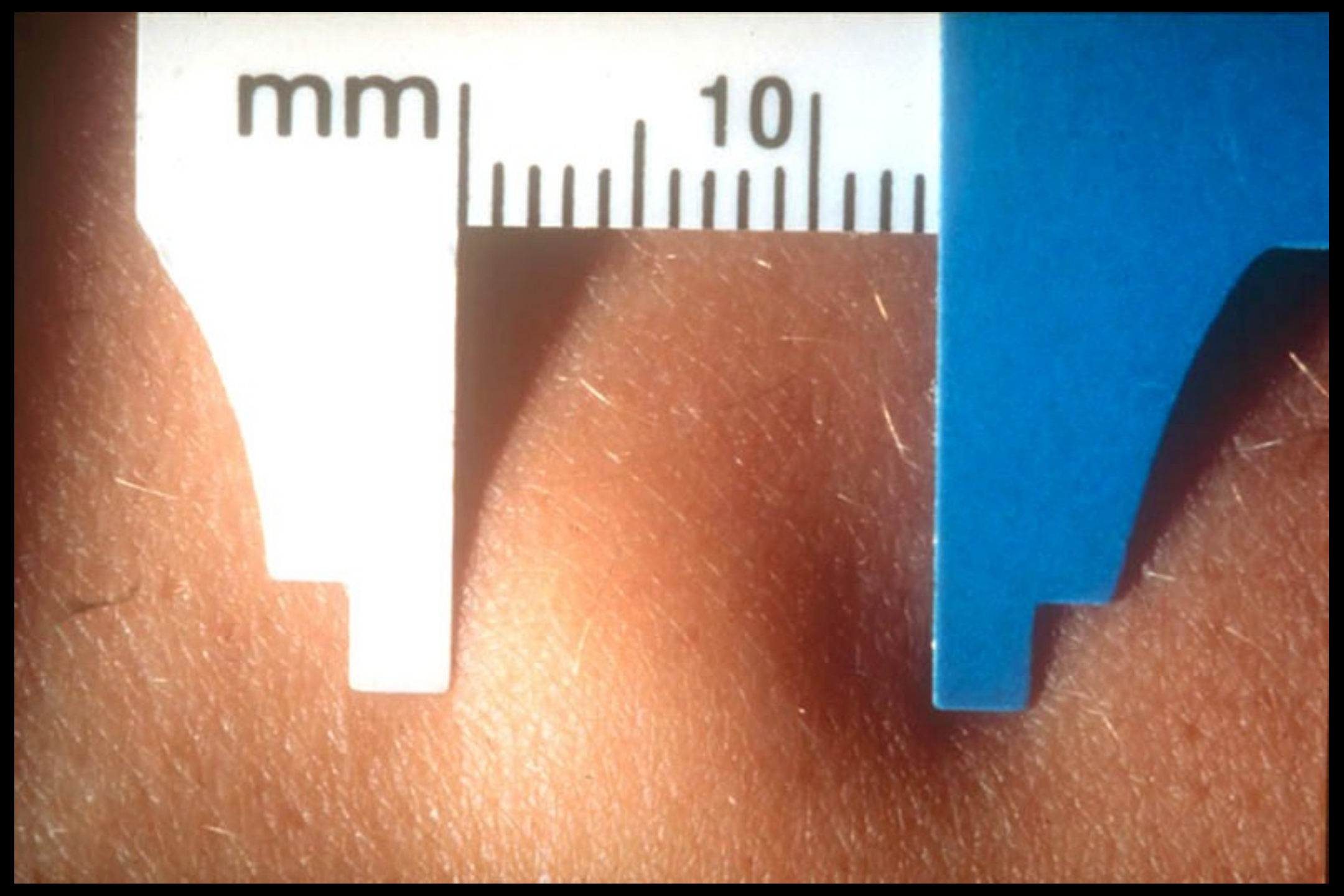
U.S. Anthrax Vaccine
Efficacy - Species Variation

Ames Strain Aerosol Challenge:

- Mice not protected at all
- Guinea Pigs are partially protected
- Rabbits and Monkeys are completely protected

U.S. Anthrax Vaccine
Adverse Reactions

- **Mild local reactions: 30% (1-2 cm erythema)**
- **Moderate local reactions: 4% (>5 cm erythema)**
- **Severe local reactions rare (edema, arm motion limited)**
- **Systemic reactions (transient) : < 0.4% (malaise, fever)**
  - ✓ **< 0.2% in MDPH data**
- **Subcutaneous nodules: 35-50%**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U.S. Anthrax Vaccine
Contraindications/Precautions

- **Permanent Exemption**
  - ✓ hypersensitivity reaction to a previous dose
  - ✓ HIV
  - ✓ age < 18 or > than 65 years
- **Temporary Exemption**
  - ✓ pregnancy
  - ✓ immunosuppressive Rx (e.g. corticosteroids)
  - ✓ active infection (URI, etc.)

Other Anthrax Vaccines

- **Live attenuated spore vaccines**
  - ⋆ **veterinary use - U.S.**
  - ⋆ **human use - Russian vaccine (STI)**
- **Culture filtrate vaccine (PA)**
  - ⋆ **U.K. vaccine similar to U.S. vaccine**
- **Candidate vaccines:**
  - ⋆ **recombinant PA**
  - ⋆ ***B. subtilis*** **cloned with PA gene**

Anthrax Strains
Genetic Engineering

- State Research Center for Applied Microbiology, Obolensk, Russia
- First known genetically engineered BW agent
- Two non-anthrax genes integrated into genome
  - ✓ cereolysin A & B genes from *B. cereus*
  - ✓ conferred hemolytic properties
- Recombinant organism defeated live vaccine (STI)

Vaccine, 1997; Vol. 15, No. 17/18: 1846-1850.

Anthrax
Summary

- Anthrax is a significant threat to our forces
- Initial presentation is clinically unremarkable
- Antibiotic prophylaxis is effective
- Anthrax vaccine is safe and effective
- Personal protective measures are still important

U.S. Anthrax Vaccine
Preparation

- Culture supernatant of attenuated, non-encapsulated strain V770-NP1-R adsorbed to aluminum hydroxide
  - ✓ filtered through 0.22 micron filters
  - ✓ contains 0.0025% benzalkonium chloride and 0.02% formaldehyde
- Composed primarily of protective antigen (PA)
  - ✓ traces of LF and EF

AVIP
Statistics through 20 Oct 98

- >258,000 total doses administered
- 96,163 service members immunized
- 43 refusals
  - ✓19 AF, 7 Army, 14 Navy, 3 DoD Civilian
- 12 VAERS forms filed
  - ✓1 Guillan-Barre Syndrome
  - ✓11 local reactions
  - ✓all 12 RTD

U.S. Anthrax Vaccine
Efficacy - Animal Trials

- **Rhesus monkeys vaccinated at 0 and 2 weeks followed by aerosol challenge with Ames strain spores:**
  - ✓ **8 weeks later with 437 LD_{50}'s**
    - ⋆ **10/10 survived**
  - ✓ **38 weeks later with 203 LD_{50}'s**
    - ⋆ **3/3 survived**
  - ✓ **2 years later with 330 LD_{50}'s**
    - ⋆ **7/8 survived**

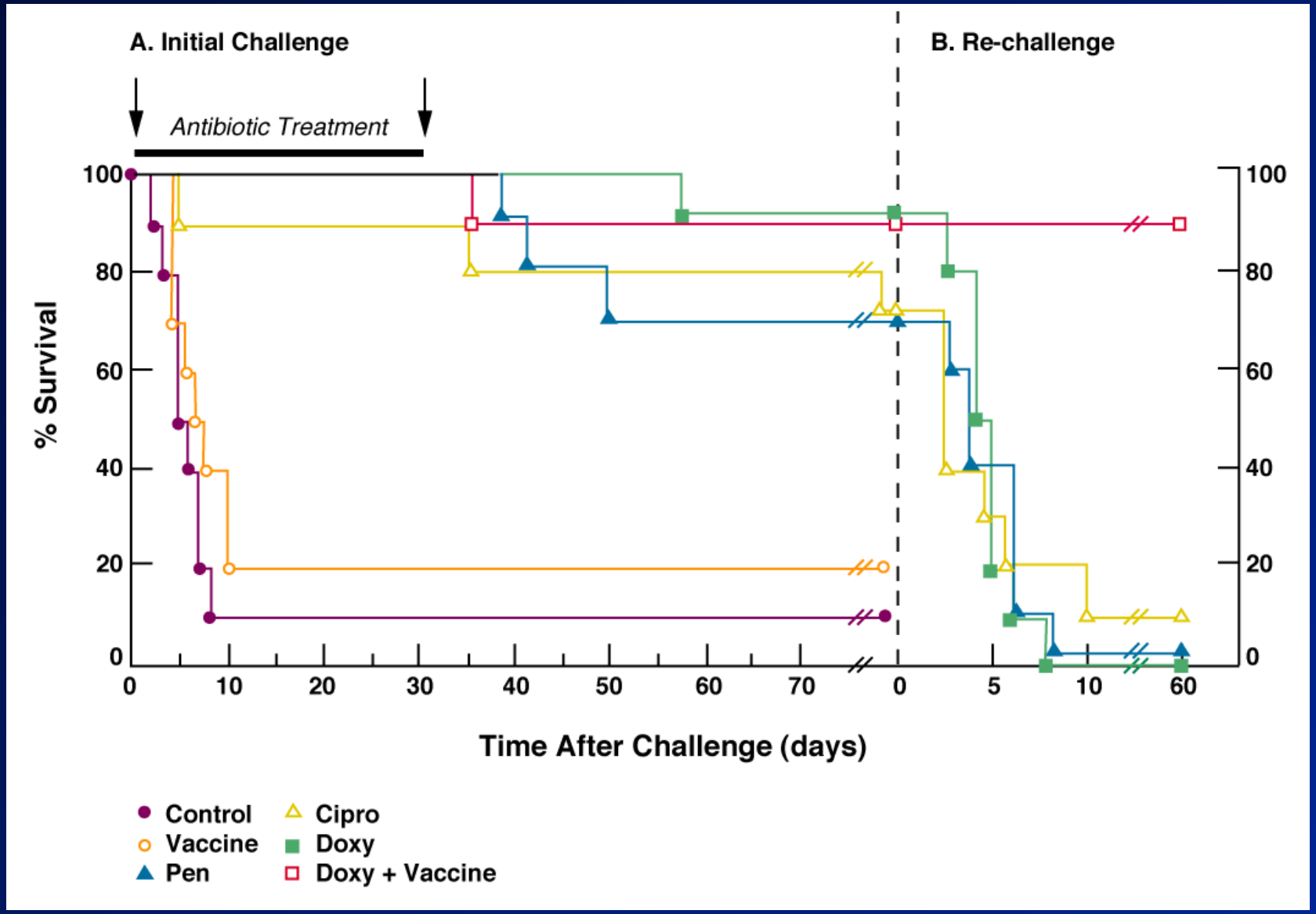
Ivins, B., et. al., *Salisbury Med. Bulletin*, 1996: Special Suppl. 87, 125-6

U.S. Anthrax Vaccine
Efficacy - Animal Trials

- **Rhesus monkeys vaccinated with one dose vaccine followed by aerosol challenge six weeks later with 93 LD_{50}'s Ames strain spores:**
  - ⋆ **10/10 survived**

  Ivins, B., et. al., *Vaccine,* 1998: 16, 1141-1148.
- **Other studies have shown in both monkeys and rabbits, two doses of U.S. Anthrax vaccine have provided complete protection against aerosol challenges with Ames strain spores**

Post Exposure Prophylaxis



Friedlander AM, Welkos SL, Pitt MLM et al., J Infect Dis 1993;176:1239-42